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EDITORIAL COMMENT

When Should We Go With HALT?*

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Transcatheter aortic valve replacement (TAVR) is an alternative to surgery for high-risk patients with severe aortic stenosis and may also be applicable in patients at intermediate surgical risk (1). Operator experience and technical improvements have reduced procedural complications, and longer term outcome data are becoming available (2). Ischemic stroke during deployment of the prosthetic valve in approximately 3% to 5% of cases (2,3) has been attributed mainly to embolism of fibrocalcific material from the surface of the diseased native valve, atheroma disease of the aortic arch traversed by the catheter, or formation of thrombus during catheter manipulation. After the procedure, clinically overt valve thrombosis has been reported with and without obstruction to blood flow, although the long-term implications of this phenomenon are not well understood (4,5). Contrast-enhanced multidetector computed tomography can detect thrombus formation on bioprosthetic valves inserted either surgically or by catheter-based intervention (6,7). Although prosthetic valve thrombosis seldom causes overt obstruction of left ventricular outflow, hypoattenuated leaflet thickening (HALT) is more common and may represent an early marker of leaflet thrombosis (4). The clinical implications and natural history of HALT, however, are currently uncertain.

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Mounting evidence supports the view that HALT represents a stage in the development of prosthetic valve thrombosis. Although there are several potential causes of leaflet thickening, including extension of fibrosis and calcification from the leaflets of the degenerated native valve into or around the prosthesis, the rapidity with which HALT appears after deployment suggests otherwise. Restricted leaflet motion (RLM), described in conjunction with HALT, fits the characteristic features of valvular thrombosis (8) and supports a unified cause of HALT and RLM. The geospatial alignment of RLM and HALT on the prosthetic valve leaflets reported by Yanagisawa et al. (9) in this issue of *iJACC* is one more fact supporting causal continuum mediated by thrombosis.

Risk factors for HALT identified by Yanagisawa et al. (9) are similar to those described by Hansson et al. (4). Two of these factors, male sex and larger bioprosthetic valve diameter, may be related, as men have on average a larger outflow tract diameter, valve annulus, and sinus of Valsalva volume that typically accommodate a larger prosthesis than that for women. A greater valve orifice area may be associated with lower transvalvular systolic pressure gradient and blood flow velocity than that generated across smaller valves, and the larger surface area may also predispose to thrombus deposition. That all of the cases of HALT reported by Yanagisawa et al. (9) involved the lower-pressure aortic side of the leaflets beginning near the bottom, fixed edges of the cusps support the hypothesis that a static local environment contributes to thrombus formation, reflected as leaflet thickening.

A crucial clinical implication of this interpretation of the disease process is whether the appearance of HALT in a post-TAVR patient responds to anticoagulation. Once RLM develops, anticoagulation may be more protective against thromboembolism than antiplatelet therapy, and the new findings regarding HALT point to the possibility that anticoagulation may be useful at an earlier stage. Patients who have received anticoagulation therapy have a lower likelihood of developing either imaging finding than those on antiplatelet therapy, and both phenomena seem to regress during treatment with warfarin, whereas persistence or progression may otherwise occur (4,8). This response to anticoagulation argues strongly that thrombosis is an integral component, if not the sole mechanism responsible for HALT and RLM.

Yanagisawa et al. (9) also report that serum levels of D-dimer, a laboratory marker of thrombosis that

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reflects degradation of fibrin, was observed to become elevated during follow-up examinations in patients developing HALT. It is difficult to distinguish cause from effect, whether elevated D-dimer levels predispose to thrombus formation through activation of the coagulation system or degradation of leaflet thrombus produces elevated levels of the biomarker, but either way, the association strengthens the view that thrombosis is linked with HALT. Taken together, the imaging observations, pathophysiology, laboratory measurements, and outcomes of treatment lead us to conclude that HALT is probably a marker of prosthetic valve thrombosis following TAVR, but histopathological confirmation is required to definitively make this connection.

The conundrum of causality shrinks before the clinical uncertainties, as it is still not clear whether the appearance of HALT without RLM is associated with adverse clinical outcomes, including stroke, other vascular complications, or hemodynamic dysfunction of the aortic valve prosthesis. Earlier studies found an association between RLM and stroke or transient ischemic attack following TAVR (8). The preponderance of limited evidence supports anticoagulation therapy for 3 to 6 months following surgical implantation of bioprosthetic heart valves to reduce the risk of thromboembolism (10), and collectively, emerging data on HALT and RLM enhances our knowledge of what can happen to those deployed by using TAVR, considering the considerable differences in designs. Yanagisawa et al. (9) found no differences between rates of stroke, transient ischemic attack, myocardial infarction, functional status, or mortality in patients with or without HALT after 1 year. Even in patients who had not undergone anticoagulation therapy, there were no clinically evident cerebral ischemic events. Although the absence of observed thromboembolic events is reassuring, HALT regressed in only 1 patient; in the remainder of the untreated patients (9 cases) serial imaging showed stable or progressive leaflet abnormalities. This leaves unsettled the issue of whether patients with subclinical HALT would benefit from anticoagulation, and larger studies are needed to understand the long term implications and optimum antithrombotic management.

The optimum timing, intensity, and duration of anticoagulation have not been established, and studies using repeated imaging to assess resolution of thrombosis may help define these components of management strategies for patients undergoing TAVR, which may vary based on the type of prosthesis as well as patient factors. At this point, the risk of developing prosthetic valve thrombosis after TAVR does not seem high enough to warrant anticoagulation therapy for every patient, particularly as candidates for TAVR typically have comorbidities that place them at risk of bleeding complications even during dual antiplatelet therapy (11). Anticoagulation therapy is necessary for patients experiencing clinical thromboembolism and for those with overt, obstructive prosthetic valve thrombosis to reduce the risks of heart failure and stroke (4). In patients with a low risk of bleeding, anticoagulation therapy with warfarin seems reasonable, aiming for an international normalized ratio (INR) of 2.0 to 3.0. For those at a high risk of bleeding, anticoagulation therapy must be used more cautiously. Whether the target-specific oral anticoagulants could be used in this situation has not been studied.

Patients at high risk of thrombotic complications, including those with impaired renal function and/or elevated D-dimer levels, should perhaps undergo early imaging to detect the development of HALT, RLM, or overt obstruction, although the exact timing has not been established. Although HALT was detected in 7% of patients between 1 and 3 months after TAVR, the incidence may be doubled (14%) at 1 year (4). Before clear recommendations can be developed, it will be necessary to clarify the long-term implications of HALT, the optimum intensity and duration of anticoagulation, and additional features of patients, valve types, and deployment protocols that most often predispose to valve thrombosis. However, continued advances in imaging are already changing the way we approach antithrombotic therapy for patients undergoing TAVR.

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